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Measles Vaccine Gamma Globulin

IN THE PREVENTION OF CROSS INFECTION WITH MEASLES IN AN ACUTE PAEDIATRIC WARD

BY

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In the paediatric wards of African hospitals in Rhodesia cross-infection with measles is still a serious problem, associated with high morbidity and mortality. The ideal solution to this problem would be wide-spread immunisation of the child population against measles, but this goal seems unattainable in the near future because of considerations of economics and manpower. An alternative solution is the immunisation of patients on admission to hospital, but though the safety and effectiveness of live virus vaccine is widely accepted, its use in acutely ill children is still debatable. Arguments against its use are that reaction to the vaccine may be detrimental to an already ill child, that in the presence of acute illness and malnutrition a good antibody response may not be obtained, and that vaccination may not be carried out early enough to prevent infection. The present study was carried out to test the validity of these arguments, and included an assessment of the protection afforded by pooled human immune globulin, which is often recommended for children in whom it is felt to be unsafe to use live virus vaccination.

Material and methods

When the study was started in May, 1968, measles vaccine was not normally available to Mpilo Hospital. However, 100 doses of vaccine (live attenuated Schwartz strain, "Mevilin-L", Glaxo), which was about to reach its expiry date, became available, and it was decided to use this in a single-blind controlled trial. As only a limited number of patients could be vaccinated there was no ethical objection to withholding vaccine from the control group.

All patients admitted to the paediatric unit were included in the study if they were between the ages of six months and 35 months (inclusive), had not had measles, were not thought to have measles on admission, and were alive on the morning following the day of admission. The last condition was a practical necessity, but did result in the exclusion of a number of very ill patients. The vast majority of patients were admitted for malnutrition, acute infection, or both, and none were excluded because of the nature or severity of their illness. Patients were assigned consecutively to one of three treatment groups:

1. Human immune globulin (Gamma Globulin, South African Institute for Medical Research), 2 ml. by intramuscular injection on the day after admission, repeated at 3-weekly intervals until discharge.
2. No treatment.
3. Measles vaccine, 1 dose by intramuscular injection on the day after admission.

All assessment of the patients was carried out by the author, who was not aware of the treatment code, which had been assigned by a colleague and given to the senior ward sisters, who carried out all treatments. Arrangements were made so that the code would not be inadvertently broken by requests for ordering of vaccine or written records on the treatment charts. Patients were observed for signs which might indicate vaccine reactions or natural measles, viz. pyrexia, rash, Koplik's spots and conjunctivitis. On discharge all patients who had not contracted measles were requested to attend for follow-up one week and two weeks after discharge in addition to any normal attendances

which were indicated. More frequent attendances were required in patients who were discharged while still being observed for vaccine reactions. Any patient who was not completely well at the two week follow-up was seen again until there was no further suspicion of their developing measles. No long term follow-up was considered practicable.

As the early months of the study coincided with an exceptionally severe epidemic of measles, an unusually high proportion of admissions had or had recently suffered from measles, so that cases were accumulated rather slowly. The study was discontinued for a period of 31 days when the author was on leave and was concluded in June 1969, thus covering a period of just over 13 months. Two doses of vaccine were wasted by being given to non-susceptible cases, leaving 98 cases in group 3. Group 2, the control group, also consisted of 98 cases, but Group 1 contained only 95 cases as stocks of globulin were exhausted shortly before the conclusion of the study. The status of cases included in and excluded from the series is summarised in Table I.

The age distribution and the main diagnoses included in the three groups are summarised in Tables II and III respectively, from which it can be seen that no major bias is likely to have been introduced by these variables.

Table I

Total cases admitted under the age of 3 years		2090
Excluded: Died on first day of admission		197
Less than 6 months of age		392
Diagnosed as measles on admission		163
Discharged or transferred to other wards on day of admission		114
History of previous measles		933
		1799
Included in study: Group 1		95
Group 2		98
Group 3		98
		291

Table II

AGE DISTRIBUTION OF THE THREE STUDY GROUPS

Age in months	Number of cases Group 1	Group 2	Group 3
6-11	40	39	46
12-17	29	40	33
18-23	12	11	13
24-35	14	8	6

RESULTS

The data obtained were analysed to determine the incidence and severity of vaccine reactions, the contribution of vaccine reactions to death and deterioration of patients, and the degree of protection against measles contracted in the ward afforded by vaccine and globulin. No attempt was made to assess long term protection from measles and no serum antibody studies were possible.

Vaccine reactions (See Table IV)

It was arbitrarily assumed that reactions were most likely to occur eight to 16 days after admission to hospital, and though this is not necessarily accurate, minor variations in the period chosen would not materially change the results. Cases who had developed measles or died before the eighth day were excluded, and those who were discharged before the sixteenth day were only included if they attended for follow-up at least on alternate days during the period of an expected reaction. Patients who developed measles during the "reaction period" presented a problem, as they could have had either natural measles or severe vaccine reactions. However, in the event, this was not important as only one such case had received vaccine.

Table IV shows the numbers of patients in the three groups who developed pyrexia, showed a probable vaccine reaction or suffered exacerbation of their illness over the reaction period. Differences between the groups were small, and by the chi square test failed to show even suggestive levels of statistical significance. The value of the "blind" technique was shown by the diagnosis of vaccine reaction in five cases who had not received vaccine! The four "reactions" observed in the

Table III

MAIN DIAGNOSIS OF PATIENTS IN THE THREE STUDY GROUPS

Diagnosis	Group 1	Group 2	Group 3
Gastroenteritis	36	38	43
Bronchopneumonia	30	30	27
Malnutrition	11	13	12
Meningitis (including TB), Encephalitis	6	1	2
Other respiratory tract infections	5	8	4
Malaria	2	0	2
Anaemia	1	2	1
Congenital heart disease	0	2	1
Acute leukemia	0	1	1
Other: Osteomyelitis, Poliomyelitis, Septicaemia, Mental retardation, Unknown	5	3	5

globulin group may well have been natural measles modified by the globulin.

It has been suggested by Lightwood (1967) in Harare Hospital that vaccine reactions have occasionally contributed to the death of a very sick child. However, the figures quoted in Table IV do not support this suggestion either for death in the reaction period or later. Even without comparison with the control group, it is unlikely that the vaccine would have been implicated in the deaths in our vaccinated group, as the one occurring in the reaction period was associated with septicaemia, pyaemic abscesses and inferior vena caval thrombosis — surely sufficient to explain death, and the later deaths were due to relapse of bronchopneumonia which had appeared to improve for some time after the sixteenth day.

Protection against measles. (See Table V.)

It was assumed that measles diagnosed on the tenth day after admission or later had been contracted in the ward. This assumption was again arbitrary, but seems to be borne out by our results. Measles diagnosed after the sixteenth day was almost certainly contracted in the ward, and so has been tabulated separately. Cases developing measles before the tenth day were probably incubating the disease when they were admitted and so have been excluded. Cases who were not known to have measles but died or were lost to follow-up might have developed measles and so could not be used to assess the protection of vaccine or globulin and were excluded.

It is apparent from Table V that very few cases developed measles after vaccination compared with a very large number in the control group and an intermediate number in the globulin group. The overall risk of contracting measles in the three groups was:— vaccine: 2.0-2.9 per cent.; globulin: 13.7-19.1 per cent.; control: 34.0-46.6 per cent. A more accurate comparison between the groups can be based on the data of Table VI. Measles developing on the tenth to sixteenth day in hospital might have been confused with vaccine reactions, though this turned out to be possible in only one case, and might represent disease already incubating on admission. Even with these reservations the protective effect of both vaccine and globulin is shown to be significant, while there were too few cases to compare vaccine with globulin. Cases developing measles after the sixteenth day diagnosed in the ward and after discharge were combined for the purpose of analysis. Again the protective effect of both vaccine and globulin was highly significant, but in these the difference between vaccine and globulin was also highly significant. On combining the figures for all cases of measles on the 10th day or later, the superior protection of vaccine compared with globulin was again demonstrated.

Of the 80 cases at risk in the control group who were known not to have died, 11 (13.7 per cent.) were re-admitted because of measles or its sequelae, against four (4.8 per cent.) of the globulin group and two (2.2 per cent.) of the vaccine group. Thus protection by vaccine or globulin reduces the load on a busy paediatric ward by reducing the number of admissions. Twelve deaths occurred in the 34 cases of measles in the control group, giving a mortality of 35.3 per cent. This high mortality presumably results from the superimposition of measles on the other illnesses from which these children were suffering. There were insufficient cases to draw definite conclusions on the mortality of measles in the vaccine and globulin groups, but in these groups as a whole a significant reduction in the death rate was effected by vaccine or globulin. There were too few cases to compare the vaccine and globulin groups in this respect.

Modified measles

A mild illness with rash, pyrexia and Koplik's spots was observed in seven cases, and was presumed to represent modified measles, though before the treatment code was broken five of these were considered to be vaccine reactions. One was a nine-month-old child in the control group in whom an attack of natural measles might have been modified by late persistence of maternal antibodies. Four had received globulin, and were presumably natural measles modified by the globulin. In the vaccine group one case developed on the twelfth day, and it is impossible to be sure whether this was a vaccine reaction or natural measles modified by vaccine given early in the incubation period; one developed on the thirty-sixth day in an 11-month-old malnourished child and was presumably natural measles modified by incomplete immunity produced by vaccination. Without virus culture and antibody determinations one cannot, of course, exclude the possibility that any of these illnesses were due to other viruses mimicking measles.

Length of stay in hospital

If there had been significant differences between the three groups in duration of hospitalisation, the risk of contracting measles might have differed between them. However Table VII (a) shows that there were actually more early discharges in the control group, thus strengthening rather than invalidating our results. The incidence of measles had little overall effect on the figures for length of stay in hospital, as the delay in discharge due to cases contracting measles was offset by the increase in deaths and transfers to the isolation hospital in these cases.

Duration of exposure and risk of contracting measles. (Table VII (b).)

Though not strictly relevant to the study, it is of interest to see when in their stay in hospital patients contracted measles. Because of uncertainty about the duration of the incubation period, accurate figures cannot be quoted, but it appears that the majority of cases were infected in their first week in hospital. However, despite the number at risk being rapidly reduced by discharges, cases were still being infected in their fourth week in hospital. Only after about five to six weeks' exposure to the ward does one seem to reach the stage where most of the susceptible patients have acquired the infection. This has the practical implication that to attempt to avoid infection by early discharge of cases is practically useless, and yet it cannot be assumed that because a child has been in the ward for several weeks without developing measles he is immune.

It is interesting that when patients are closely observed a prodromal illness lasting eight to 15 days can often be distinguished. In some cases this took the form of an initial pyrexia with upper respiratory infection, followed by a period of apparent normality until the onset of clinical measles; in others there was gradually increasing illness and pyrexia through the whole incubation period, the nature of which was obscure until finally measles developed.

Table IV

DATA RELEVANT TO THE OCCURRENCE OF POSSIBLE VACCINE REACTIONS IN THE THREE STUDY GROUPS

	Group 1	Group 2	Group 3
Cases excluded:—			
Measles developed on 1-7th hospital day	1	1	0
Died on 1-7th hospital day (excluding death associated with measles)	3	2	3
Discharged before 16th hospital day and inadequate follow-up	16	15	19
Measles developed on 8-16th hospital day	2	12	1
Total cases excluded	22	30	23
Cases remaining	73	68	75
Pyrexia on 8-16th hospital day (excluding cases of measles) 100° - 102°F.	12	13	16
more than 102°F.	11	7	10
Probable vaccine reaction, i.e. rash and pyrexia (excluding measles cases)	4	1	3
Exacerbation of illness on 8-16th hospital day (excluding cases of measles and deaths)	14	9	13
Deaths on 8-16th hospital day (not associated with measles)	2	2	1
Deaths later than 16th hospital day (not associated with measles)	2	1	2

Table V

MEASLES IN THE THREE STUDY GROUPS

	Group 1	Group 2	Group 3
Cases excluded:—			
Measles developed on 1-9th hospital day	1	1	0
Died on 1-9th hospital day (not associated with measles)	3	3	0
Died on 10th day or later (not associated with measles)	4	2	6
Did not develop measles in ward but lost to follow-up	19	19	22
Total cases excluded	27	25	28
Cases remaining	68	73	70
Measles (in ward or on follow-up) on 10-16th day	2	12	1
Measles in ward later than 16th day	4	8	0
Measles on follow-up, later than 16th day, within two weeks of discharge	7	14	1
Re-admissions associated with measles or sequelae of measles contracted in ward	4	11	2
Death associated with measles developing on 10th day or later	3	12	1
Modified measles on 10-16th day	3	1	1
Modified measles after 16th day	1	0	1

Table VI

STATISTICAL SIGNIFICANCE OF DIFFERENCES BETWEEN NUMBERS OF CASES CONTRACTING MEASLES IN THE THREE GROUPS. RESULTS OF CHI SQUARE TESTS ON DATA OF TABLE V, VALUES OF P. (N.S. = NOT SIGNIFICANT).

	Values of p in comparison of groups		
	1 and 2	2 and 3	1 and 3
Measles on 10-16th day	$< .01$	$< .005$	N.S.
All measles later than 16th day	$= .05$	$< .005$	$< .005$
All measles on 10th day or later	$< .005$	$< .005$	$< .005$
Deaths associated with measles developing on 10th day or later	$< .025$	$< .005$	N.S.

Table VIII

(a) LENGTH OF STAY OF CASES IN HOSPITAL. (b) INTERVAL BETWEEN DAY OF ADMISSION AND DAY ON WHICH DIAGNOSIS WAS MADE IN CASES WHO DEVELOPED MEASLES.

Hospital days	(a) Number of cases discharged or died			(b) Number of cases who developed measles		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
0 - 4	9	10	6	1	0	0
5 - 8	29	31	27	0	1	0
9 - 12	21	13	22	0	2	0
13 - 16	11	9	10	2	10	1
17 - 20	1	7	8	4	9	0
21 - 24	8	7	4	5	3	1
25 - 28	6	7	6	2	3	0
29 - 32	5	4	4	0	3	0
33 - 36	1	2	0	0	3	0
37 - 40	1	1	1	0	1	0
more than 40	3	7	10	0	0	0

DISCUSSION

There is ample documentation (Krugman and Ward, 1964) of the effectiveness and safety of measles vaccine in field trials and institutionalised patients, including those suffering from tuberculosis, but there are hardly any reports of its routine use in acutely ill children. In fact, acute illness of any kind or any degree of severity is listed as a contra-indication to vaccination in the literature supplied with the Glaxo vaccine and all others known to the author. A trial similar to ours was reported by Wagstaff from Baragwanath Hospital, Johannesburg, dealing with a series of 312 cases of whom 214 were vaccinated. This study which was initiated at about the same time as ours, differs in that there was no control group in the same ward, thus reducing the exposure to infection of the cases studied, some cases were excluded on the grounds of severe illness, antibody levels were determined, though these seem to have introduced complication as much as illumination, and human immune globulin prophylaxis was not studied. Wagstaff's findings will be discussed further with our own results.

The questions we set out to answer were whether in our patients vaccine might be detrimental because of co-existing illness, and how effective a protection against ward cross-infection with measles would be achieved, whether by vaccine or globulin. Far from showing detrimental effects on the patients, it is impossible to demonstrate with certainty from our results that vaccine reactions which could be clinically diagnosed occurred at all. What is certain is that until there is wide-spread vaccination of the child population measles contracted in the ward is an infinitely greater hazard than vaccination. Dr. Wagstaff reaches the same conclusion, and her figures also show that even with a large number of the ward cases being vaccinated there is still a significant risk of measles occurring in the few patients one might be tempted not to vaccinate because of severe illness.

The protection achieved by vaccination was impressive, even in these ill, often malnourished children. The incidence of measles in the vaccine group was under three per cent., against over 34 per cent. in the control group. In Baragwanath the incidence of failed vaccination was between 1.5 and 2.5 per cent. Failure of vaccination will sometimes occur in children in the six to nine month age group because of persistence of maternal anti-

bodies; one of our failed cases was eight months old, and in Baragwanath cases of six and seven months were observed. However, having seen several cases of florid measles at five months, with one death, we now vaccinate from five months of age. Antibody determination would be helpful in these cases, and a later repeat vaccination would be advisable in some of them. It must also be borne in mind that passive immunity mediated by blood or plasma transfusions will have a similar effect in preventing effective vaccination. Malnutrition and/or acute illness may well affect the immune response to measles and vaccine virus, and this is supported by findings in Baragwanath that patients with antibody titres of 20 or even 40 developed measles, when by normal criteria they should be immune. On the other hand there is evidence that malnourished patients respond normally to attenuated measles virus, even when given with gamma globulin (Scrimshaw, *et al.*, 1968). Even with antibody studies Dr. Wagstaff was unable to comment on the likelihood of good long term protection being given by vaccination in these circumstances, and we have no data as yet on this problem.

The protection afforded by globulin was also evident in comparison with the control group, but was significantly less than that of vaccine. In view of the short-lived nature of the protection, and the apparent safety of vaccine, there seems to be little reason to use globulin except in cases of immunological defect and malignancy. There might be an argument for using globulin in an exceptionally ill patient, as our conclusions are based on too few cases to affirm that vaccine reactions will never have serious ill-effects on such a patient. However, it seems likely that even in such a case the risk of developing measles after receiving globulin is still significant and is greater than the risk of a severe vaccine reaction.

It is difficult to be sure of the reason for failure of globulin to prevent or even to produce significant modification of measles in so many of our cases. The dose given was well above the 0.02 ml. per pound body weight generally recommended (Krugman and Ward, 1964), but, of course, the titre of measles antibody in any particular batch of globulin is unknown. The time of peak incidence of measles in the control group suggested that the majortity of cases were infected during their first week in hospital, whereas the globulin group were infected somewhat later, the majority towards the end of the second week. Thus though the globulin is said to be effective for at least four weeks (Krugman and Ward, 1964), it is possible that in the presence of the catabolic state of acute infection and the disordered protein metabolism of malnutrition, antibody levels dropped more rapidly than would be expected, permitting infection to occur before the second dose was given on the twenty-first day. There is some evidence that the effect of passive immunity mediated by exogenous gamma globulin administration is modified by protein malnutrition (Scrimshaw *et al.*, 1968). The complete lack of cases occurring in the globulin group after the twenty-eighth day suggests that many of the remaining cases were immune due to subclinical or modified infection before that time. These conclusions are speculative, and would require a larger study, preferably with determination of antibody levels for confirmation. We feel that in our circumstances it would be unethical to enlarge on the present study with any trial involving a control or globulin group, as our results already show beyond reasonable doubt that it is our duty to protect our patients with vaccine, which has now become available for routine use.

SUMMARY

In an acute paediatric ward in which measles infection was endemic three groups of children aged six to 35 months were given measles vaccine, gamma globulin or no prophylactic treatment against measles. Data are presented on the incidence of measles and vaccine reaction in these patients. The following conclusions were reached:

1. Measles vaccine given on the day after admission almost completely prevented cross-infection with measles.
2. Gamma globulin approximately halved the incidence of cross-infection with measles and reduced its severity in many infected cases.
3. Reactions to measles vaccine did not constitute a significant risk even to severely ill and malnourished patients.

The overall conclusion was that in the circumstances of this study, vaccination against measles of susceptible children, even if they are acutely ill and malnourished, is not only justified but is mandatory.

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